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PATENT

Attorney Docket No. 2307AA-031220US
Client Ref. No.: 90-160-5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Steinunn Baekkeskov et al.

Application No.: 08/838,486

Filed: April 7, 1997

For: IMPROVED METHODS FOR THE
DIAGNOSIS AND TREATMENT OF
DIABETES

Examiner: Gerald R. Ewoldt

Art Unit: 1644

APPELLANTS' BRIEF (REVISED) UNDER 37
CFR §1.192



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Sir:

In response to the final office action of July 29, 2003 and further to the notice of appeal filed December 29, 2003, appellants submit the following brief.

I. REAL PARTY IN INTEREST:

The Regents of the University of California and Yale University, jointly.

II. RELATED APPEALS AND INTERFERENCES:

USSN 08/452,053 ('053 application), the parent of the present case contains claims to methods of diagnosing insulin dependent diabetes mellitus (IDDM) using glutamic acid decarboxylase (GAD). Applicants have requested an interference between the '053 application and US 5,645,998 ('998 patent) assigned to the University of Florida, which has substantially corresponding claims. The '053 application was allowed and prosecution suspended pending declaration of the requested interference. Recently prosecution has been reopened with a new

office action. Applicants have responded to the office action and maintain the request for interference.

The present case, which is directed to methods of treatment and pharmaceutical compositions substantially corresponds at least in part to claims to two other patents assigned to the University of Florida, US 6,001,360 ('360 patent), and US 5,762,937 ('937 patent). The '360 and '937 patents are in the same priority lineage as the Florida '998 patent. The disclosure of these patents is substantially similar to that of the present case, and as noted in the request for interference filed May 5, 2003, the earliest conceivable effective filing date of the '360 and '937 patents and that of the present application are only three weeks apart. The '937 Florida patent is cited by the Examiner as anticipating many of the claims present in the present case. An exemplary claim from the '360 Florida patent appears below.

1. A method for preventing or delaying the development of clinical symptoms of insulin dependent diabetes wherein said method comprises administering to an animal an essentially pure GAD protein or a fragment thereof which, when administered to an animal, prevents or delays the development of clinical symptoms of insulin dependent diabetes.

Applicants have requested that an interference be declared between the present application and US 6,001,360, and US 5,762,937 under 37 CFR 1.607 and 1.608 (see paper no. filed May 5, 2003). The Examiner has declined to consider this request pending resolution of the issues posed by this appeal. The priority issues for the diagnostic claims in the parent and therapeutic claims and therapeutic claims in the present case involve the same underlying facts vis a vis the University of Florida patents. Therefore, in the interest of judicial economy, it is requested that the relative priority between the present case and the Florida '360 and '937 patents and the relative priority between the '053 parent of the present case, and Florida '998 be resolved as first and second counts of the same interference.

III. STATUS OF CLAIMS:

Claims 31, 35, 50-57, 59 and 62-67 are pending and rejected. Claims 1-30, 32-34, 36-49, 58, and 60-61 are cancelled. All rejected claims are appealed.

IV. STATUS OF AMENDMENTS:

An amendment after final was filed canceling claims 49 and 58 and has been entered. All previous amendments have been entered.

V. SUMMARY OF THE INVENTION:

The invention is premised in large part on the discovery that glutamic acid decarboxylase (GAD) is a component of a pancreatic beta cell 64 kDa antigen that is a major autoantigen in insulin dependent diabetes mellitus (IDDM) (also known as type 1 diabetes) (specification at p. 8, lines 32-37). Whereas the pancreatic beta cell 64 kDa antigen is present in pancreatic islets in only minute amounts (specification at p. 3, lines 25-3)), GAD is present in large amounts in the CNS (p. 8, line 36). The discovery of the relationship between GAD and the pancreatic 64 kDa and consequent availability of large amounts of autoantigenic protein gave rise to diagnostic and therapeutic methods of detecting and treating IDDM using GAD (see specification at p. 9, lines 9-14). The diagnostic methods are claimed in the '053 parent application. The therapeutic methods and pharmaceutical compositions are claimed in the present case.

Specifically, independent claim 31 is directed to a method for inhibiting the development of insulin dependent diabetes mellitus by administering to a patient a therapeutically effective dosage of GAD (specification at pp.19-22). Administration of GAD to a patient induces tolerance to the 64 kDa pancreatic autoantigen, thereby inhibiting further destruction of beta pancreatic cells and the clinical symptoms of IDDM that eventually result from this destruction.

Independent claim 62 recites a similar method of treatment except that the wording and format of claim 62 was specifically chosen to follow that of claim 1 from the Florida '360 patent as closely as possible for purposes of interference.

Independent claim 35 recites a composition comprising GAD, which is at least 99% w/w pure, in a pharmaceutically acceptable carrier for parenteral administration to a human patient (specification at pp. 19-22 and p14, line 13).

Dependent claims 54 and 59 specify that the GAD used is lower molecular weight GAD. GAD exists in two forms known as lower and high molecular weight forms, now known as GAD65 and GAD67 respectively (see e.g., specification at p. 37, lines 17-23).

VI. ISSUES:

1. Whether claims 31, 50-53, 62-67 lack enablement under 35 USC 112, first paragraph.
2. Whether claims 31, 64 and 65 are anticipated by US 5,762,937 under 35 USC 102(e).
3. Whether claims 35, and 54-57 are anticipated by US 5,762,937 under 35 USC 102(e).
4. Whether claims 50-53, 59, 66 and 67 would have been obvious under 35 USC 103(a) over US 5,762,937.
5. Whether claims 35 and 54-57 would have been obvious under 35 USC 103(a) over US 4,086,142 in view of US 4,736,020.

VII. GROUPING OF THE CLAIMS:

With respect to the first issue, for purposes of this appeal only, the claims subject to the rejection stand or fall together. (However, the rejection has not been applied against all claims.) With respect to the second issues, for purposes of this appeal only, the claims subject to the rejection stand or fall together. With respect to the third issue, the claims subject to the rejection do not stand or fall together. Additional arguments are presented with respect to claim 54. With respect to the fourth issue, the claims subject to the rejection do not stand or fall together. Additional arguments are presented with respect to claim 59. With respect to the fifth issue, the claims subject to the rejection do not stand or fall together. Additional arguments are presented for claims 54-57.

VIII. ARGUMENT

1. Claims 31, 50-53, 62-67 are enabled under 35 USC 112, first paragraph

a. Summary of Claimed Methods and Evidence Supporting their Enablement

The therapeutic method of the present claims is a simple one involving a single step of administering a therapeutically effective dosage of GAD to a patient. Several references published subsequent to the invention show that administration of GAD to an animal model of IDDM, a NOD mouse, is effective to inhibit IDDM (see first Baekkeskov declaration filed July

22, 2003 at paragraph (5) citing Tisch *et al.*, *Nature* 366, 71-75 (1993); Kaufman, *Nature* 366, 69-71 (1993), Tian *et al.*, *Nature Medicine* 12, 1348 (1996), Peterson *et al.*, *Diabetes* 44, 1478 (1994), and Pleau *et al.*, *J. Immunol. Immunopath.* 76, 90-95 (1995)); and Harrison, *Molecular Medicine* 1, 722-727 (1994)). A phase-I clinical trials has demonstrated that GAD can safely be administered to humans (see Press Release attached to response of January 5, 2001). A phase-II clinical trial has confirmed safety and shown statistically significant evidence of efficacy in a patients with LADA (a subset of diabetes masquerading as type II on account of its late onset but which is now regarded as a form of Type 1 diabetes (see first Baekkeskov declaration at paragraph (6) and Press Release attached to supplemental communication of July 22, 2003, second Baekkeskov declaration, submitted herewith, at paragraphs (3) to (5)).

(b) Summary of Examiner's Rationale

The Examiner acknowledges that the claimed methods are enabled with respect to their use in a NOD mouse (final office action of July 29, 2003, at p. 2). However, the Examiner denies that the methods are enabled for a patient, notwithstanding the above evidence, on several grounds. First, the Examiner says that although the NOD mouse model may be the best available model, results obtained from it are not predictive of efficacy in humans (final office action at p. 4). Second, the Examiner alleges that the results of a successful phase I safety study is insufficient to support the enablement of the present claims (office action of November 4, 2002 at p. 4). Third, the Examiner discounts the results from a successful phase II trial on the basis that these results were obtained on a related pathology of non-autoimmune origin (final office action at p. 4). Fourth, the Examiner takes the view that the general field of tolerance inducing therapies was unpredictable at the effective filing date of the application based in part on lack of a successful therapy in the 13 years post filing (office action at p. 4, 3rd paragraph) and the teaching of the specification that care should be taken that administration of compositions does not potentiate the autoimmune response (p. 20, lines 16-19). Fifth, the Examiner cites two articles (Goodnow and Marketletter) as evidence that methods of inducing tolerance that worked in animal models have not proved successful in human in two diseases other than IDDM (final office action at p. 3, last paragraph). Finally, the Examiner raises additional issues with respect to the recitation of "preventing" and "fragment" in claim 62 (office action of February 4, 2003 at pp. 4-5).

(c) The legal standard

The leading case regarding the sufficiency of animal trial to support enablement of treatment in humans under 35 USC 112, first paragraph is *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). The *Brana* court reversed a rejection under 35 USC § 112, first paragraph based on the PTO's refusal to accept data from testing compounds in an animal model of cancer (*id.* at 1444). The animal model at issue in *Brana* was formed by injecting cancer cells into mice. The PTO took the position that the model was not fully representative of human cancers because the mice did not naturally develop cancers (*id.* at 1440). The PTO argued that "in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, [meaning] in vivo testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans" (*id.* at 1142). The Federal Circuit reversed the rejection as "arbitrary and capricious." The Federal Circuit held that "Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings" (*id.* at 1442).

(d) Analysis

Here, it is not disputed by the Examiner that the presently claimed methods are enabled for an animal model of IDDM, namely, the NOD mouse. The remaining issue is whether the NOD mouse is reasonably predictive of similar results in treating IDDM in other patients, including humans. There is abundant evidence that such is the case. As explained in the declaration of Dr. Baekkeskov submitted July 21, 2003 (first Baekkeskov declaration), the NOD mouse is a good model of IDDM in human because both humans and mice develop the same pathological characteristics of autoantibodies and T-cells to GAD (first Baekkeskov declaration at paragraph 6). Moreover, positive results in the NOD mouse have been used as evidence to support human clinical trials of a number of drugs to treat IDDM, including humanized OKT3, alpha interferon, and most importantly GAD (see first Baekkeskov declaration at paragraph 6). In the case of GAD, both phase I and phase II clinical trials have been conducted. The phase I trial has provided evidence of safety, and the phase II trial has provided statistically significant evidence of efficacy. In the aggregate, the above evidence abundantly supports the conclusion that results in the NOD mouse are reasonably predictive of

similar success in humans. Even the Examiner acknowledges, the NOD mouse may be the "best available model" (final office action at p. 4).

The Examiner criticizes reliance on the phase I trial of GAD on the basis that a phase I trial cannot show freedom from long-term side effects or establish efficacy (office action of November 4, 2002 at p. 4). Appellants acknowledge that a phase I trial cannot preclude the possibility of long term side effects, nor establish efficacy. Nevertheless, the fact that a phase I trial has been allowed to occur is an indication that a disinterested body of experts (i.e., the FDA or equivalent in other countries) has concluded from the relevant preclinical data including animal models, such as those in the references cited in the first Baekkeskov declaration at paragraph (5)), that the trial has a reasonable chance of success. This unsolicited and disinterested opinion of experts in the field stands in opposition to the office action's own assessment of the animal models. The Examiner dismisses these comments regarding the opinion of a disinterested body of experts as mere attorney argument (office action of February 4, 2003 at p. 3). However, in fact appellants' comments regarding the significance of a phase I trial mirror those in the MPEP:

Before a drug can enter human clinical trials, the sponsor, often the applicant must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary.

MPEP 21707.03.

In view of the corroboration provided by the MPEP, a declaration should not be required for acceptance of appellants' position that the fact that a phase I trial has been allowed to occur is an indication that a body of experts has concluded from the relevant preclinical data including animal models that treatment in humans has a reasonable chance of success

The Examiner discounts the successful phase II trial employing GAD on the basis that it was conducted on a related pathology of non-autoimmune origin (final office action at p. 4). The notion that anyone would conduct a phase II clinical trial of GAD on patients not

suffering from autoimmune attack of GAD to whom the treatment would be of no apparent benefit is implausible, and in fact mistaken. The phase II trial was conducted on a subclass of diabetes patients termed LADA. As was stated in the materials describing the phase II trial and the first Baekkeskov declaration, the patients of this subclass of patients are suffering from autoimmune attack and do have autoantibodies to GAD, as in type I patients. A second declaration of Dr. Baekkeskov explaining the pathology in these patients and why they are representative of IDDM or type I diabetes patient is attached.

Next the Examiner points to general unpredictability in the field of inducing immunotolerance based in part in part on lack of a successful therapy in the 13 years post filing (final office action at p. 4, 3rd paragraph) and the teaching of the specification that care should be taken that administration of compositions does not potentiate the autoimmune response (p. 20, lines 16-19). Appellants initially note that the issue at hand is the enablement of claims containing a single step of administering a therapeutically effective amount of GAD to a patient. Practice of such a method is not dependent on an understanding of the entire field of immunotolerance. Second, a period of 13 years or more between the appearance of a drug in the laboratory and its final approval for use by the FDA or similar body is not unusual. In fact, the average drug development time from discovery to marketing has been reported as 14.7 years (see Findlay, *Food and Drug Law Journal* 54, 227-232 (1999) at p. 227, copy attached). Patent applications are by necessity filed at an early date in this process before public disclosure. Third, although the Examiner is correct that the present specification does indicate that care should be taken not to potentiate an immune response, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the date of the invention (see first Baekkeskov declaration at paragraph (4)). For example, a standard immunology textbook available at the priority date of the invention indicates that either low or high dosages of antigen favor a tolerogenic response, whereas intermediate dosages favor an immunogenic response (Benjamini & Leskowitz, *Immunology: A Short Course* (Liss, 1988) at p. 256).

The Examiner's criticism that the materials describing the phase II clinical trial do not describe the dosage as being "high" or "low" (final office action at p. 4) is oversimplistic. A dosage is not described as "high" or "low" in isolation. Rather, guidance that the desired

tolerogenic effect can be achieved at high or low dosage represents a principle that if the desired effect is not achieved by the initially chosen dosage, it can likely be achieved by varying the dosage. Performing clinical trials at varying dosage is standard practice in the art. As the Examiner has acknowledged "[i]t would have been prima facie obvious to one of ordinary skill at the time the invention was made to optimize the dosage of the GAD administered in the method of the reference [US 5,762,947], said optimization falling well within the purview of one of skill in the art at the time of the invention" (office action of November 4, 2000 at p. 7).

Next, the Examiner cites Goodnow and a Marketletter article, as evidence that methods of inducing tolerance that worked in animal models were a complete failures in treatment of humans with multiple sclerosis and rheumatoid arthritis (final office action at p. 3, last paragraph). Results reported for other diseases are less significant and do nothing to change the undisputed evidence that is directly applicable to insulin dependent diabetes. That is, treatment of GAD has been showed to induce tolerance in numerous independent studies on a NOD mouse model, and successful phase I and II human clinical trials have been completed. Also, it is noted that the Examiner omits to mention parts of the articles that do not support his positions. For example, the Marketletter article reports that "substantial improvements" above baseline were observed in the Collerol trial and that Autoimmune still "firmly believes in its technology."

The Examiner's allegation of inconsistency between remarks in paragraph (4) of the first Baekkeskov declaration regarding animal models and appellants' above position regarding the alleged failures in clinical trials of multiple sclerosis and rheumatoid arthritis is incorrect and an obfuscation of the real issues. It is undisputed that the presently claimed methods are enabled in an animal model. It is common sense that alleged failures in clinical trials of multiple sclerosis and rheumatoid arthritis using agents unrelated to GAD are less relevant to the claimed methods than the successful clinical trials using GAD in a subset of patients undergoing autoimmune attack of GAD.

Finally, the Examiner comments on two issues specifically applicable to claim 62, namely the recitation of "preventing" and "fragment" of GAD. Initially, it is noted that claim 62 substantially corresponds to claim 1 of US 6,001,360 from which it was copied for purposes of

provoking an interference. Claim 1 of '360 also contains the offending terms "preventing" and "fragment." Thus, the USPTO has allowed a substantially similar claim to others.

The Examiner objects to the term "preventing" on the basis that it implies "absolute prevention" which in the Examiner's view cannot be achieved (office action of November 4, 2002, sentence bridging pp. 4-5). In response, it is submitted that in the context of preventive medicine the term "preventing" is used more generally than to imply absolute prevention. Few if any preventive measures achieve absolute prevention in every patient. In any event, it is not implausible that treatment of GAD can prevent onset of clinical symptoms of IDDM at least in some patients. Clinical symptoms of IDDM do not start until the majority of β -pancreatic islet cells have been destroyed. Onset of clinical disease is preceded by a long prodromal period in which progressive destruction of β -pancreatic cells occurs and autoantibodies to GAD are present (see specification at paragraph bridging pp. 1-2 and also Tian, *Nature Medicine* 12, 1348 (1996), of record, at p. 1348). If autoantibodies are detected early in the prodromal period (using the diagnostic methods disclosed in the application) and GAD is then administered, it will not restore any pancreatic destruction that has already occurred, but will stop or inhibit further destruction. If administration of GAD is successful in preventing further destruction, and the patient does not reach the point at which sufficient β -pancreatic cells have been destroyed for clinical symptoms then diabetes has been prevented.

With respect to fragments, the Examiner alleges that claim 62 encompasses administration of fragments having only a single amino acid, which the Examiner says would be highly unpredictable (Office action of February 4, 2003 at p. 5, first paragraph). In response, it is not reasonable to construe the claims as encompassing administering "fragments" consisting of only a single amino acid. Claim 62 specifies a fragment which "when administered to the patient, prevents or inhibits the development of insulin dependent diabetes." The recital of a specific function for a fragment implies that the fragment has sufficient structure to provide that function. Therefore, claim 62 does not encompass single amino acids or other short fragments too small to achieve the desired function of preventing or inhibiting development of insulin dependent diabetes.

In conclusion, the Examiner has not met his burden of proving that successful results obtained in a mouse model (which the Examiner acknowledges is enabled by the

specification) are not predictive of similar results in other patients, including humans, particularly given the evidence from clinical trials of GAD at discussed above. At most, the Examiner argues that the NOD mouse is not a perfect model of IDDM in humans. That the NOD mouse does not mimic the human disease in every respect was also true of the mouse model in *Brana* and probably every other mouse model of human disease. As *Brana* made clear, rejection of data from a mouse model for this reason is arbitrary and capricious.

2. Alleged Anticipation of Claims 31, 64 and 65 by US 5,762,937 under 35 USC 102(e) should be Determined by Interference

For purposes of this appeal, appellants do not dispute the merits of the rejection. However, appellants do allege that they invented the above claims before the inventors of the '937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 7), this issue can be resolved only by interference. Appellants have formally requested an interference with the '937 patent, as noted above.

3. Alleged Anticipation of Claims 35 and 55-57 under 35 USC 102(e) should be Determined by Interference; Claim 54 is not Anticipated by US 5,762,937

For purposes of this appeal, appellants do not dispute the merits of the rejection with respect to claims 35 and 55-57. However, appellants do allege that they invented the above claims before the inventors of the '937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 7), this issue can be resolved only by interference. Appellants have formally requested as interference with the '937 patent, as noted above.

Appellants deny that claim 54 is anticipated by the '937 patent. The Examiner's rationale is summarized in the office action of February 4, 2003 at paragraph 15. The Examiner relies particularly on Example 14 of the '937 patent as teaching a composition comprising GAD. The Examiner says that lower molecular weight GAD is the only molecular weight GAD taught by the reference and that lower molecular weight GAD would thus inherently be present. In the final rejection, the Examiner adds that the specification refers repeatedly to the lower molecular weight antigen (the 64 kDa antigen) (final office action at paragraph 9).

In response, it is submitted that the '937 patent does not teach either expressly or under principles of inherency a composition comprising lower molecular weight GAD in at least 99% purity, as specified by claim 54 (including the elements from antecedent claim 35). Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention," *RCA Corp v. Applied Digital Data Sys. Inc.*, 2212 USPQ 385, 388 (Fed. Cir. 1984). Inherent anticipation cannot be found unless the "prior art *necessarily* functions in accordance with limitations of a process or method claim" (*In re King*, 23 USPQ 136, 138 (Fed. Cir. 1986)). "Inherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum*, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). Here, Example 14, on which, the Examiner relies, refers merely to a "purified form of the 64 K antigen" (col. 25, line 54-55). The '937 patent does not indicate that the 64 K antigen has been purified to such an extent as to give 99% pure lower molecular weight GAD.

If one were to attempt to obtain a "purified form of the 64 K antigen" from pancreatic islet cells, the Examiner has not show that one would necessarily obtain 99% purity. In fact, one would be most unlikely to do so for several reasons. One difficulty limiting purification was the small quantities of pancreatic islet cells available and the fact that of this small amount of material, that 64 kDa antigen was known to constitute less than 0.1% of total islet proteins (Baekkeskov et al., *Diabetes* 38, 1133-1141 (1989)). A second difficulty was the absence in the '937 patent of a simple and specific assay by which the yield of antigen could be assessed at each step in a purification procedure. A third difficulty was the need to achieve purification without impairing the 64 kDa antigen for subsequent use of the antigen in a pharmaceutical composition. In any event, regardless of the degree of difficulty of purifying the 64 kDa antigen from pancreatic cells, the Examiner has not met his burden of proving that a "purified form of the 64 K antigen" from pancreatic cells is necessarily at least 99% pure lower molecular weight GAD.

If one were to purify a form of the 64 kDa autoantigen from the CNS or from cells expressing recombinant GAD, one would not, based on the teaching of the patent, necessarily obtain lower molecular weight GAD rather than higher molecular weight GAD or a mixture thereof. The two forms naturally exist as a mixture in the CNS (see specification at p. 5, lines 26-28) and one would thus naturally purify a mixture of GAD unless taught to do otherwise.

The '937 patent does not provide any such teaching. If one sought to purify GAD from cells expressing GAD recombinantly one would obtain whatever form of GAD was being expressed. The '937 patent does not provide any teaching to express the lower molecular weight form of GAD recombinantly. In fact, it provides the sequence of the higher molecular weight form (see Figs. 1A, B, and C)¹.

Therefore, regardless of whether one sought to purify the 64 kDa antigen from the pancreas, or obtain GAD from its natural source or by recombinant expression, one would not following the teaching of the '937 patent necessarily arrive at a pharmaceutical composition containing at least 99% w/w pure lower molecular weight GAD.

4. Alleged Obviousness of Claims 50-53, 66 and 67 Should be Determined by Interference; Claim 59 Would Not Have Been Obvious Over US 5,762,937

For purposes of this appeal, appellants do not dispute the substance of the rejection with respect to claims 50-53, 66 and 67. However, appellants do allege that they invented the above claims before the inventors of the '937 patent. Because the rejection is made at least in part over the claims of the '937 patent (final office action at paragraph 10), this issue can be resolved only by interference. Appellants have formally requested as interference with the '937 patent, as noted above.

Claims 59 would not have been obvious over the '937 patent for analogous reasons that claim 54 is not anticipated by the above patent. Claim 59 requires that the GAD used in therapeutic methods or compositions is human GAD65 at a purity of at least 99% w/w. As discussed in connection with claim 54, such a level of purity of lower molecular weight GAD is not inherent in the reference to a purified form of the 64 kDa antigen. It would not have been obvious to purify lower molecular weight GAD to 99% purity from pancreatic cells for the reasons discussed above in connection with claim 54. It would not have been obvious to purify lower molecular weight GAD from the CNS or cells recombinantly expressing GAD based on

¹ That Fig. 1 represents the sequence of higher molecular weight GAD can be determined as follows. The '937 patent references Kobayashi et al., *J. Neuroscience* 7, 2768-2772 (1987) as the source of the sequence (see col. 18, lines 59-64). GenBank entry P14748 corresponding to the cited Kobayashi paper characterizes the sequence described by Kobayashi as GAD67.

the teachings of the '937 patent also for the same reasons discussed for claim 54. That is, the '937 patent does not provide any teaching that there are two forms of GAD much less that one should purify the lower form from the higher form in the mixture that naturally occurs in the CNS. The '937 patent also does not provide any teaching to recombinantly express the lower molecular weight form as distinct from the higher molecular weight form for which it provides the sequence.

For these reasons, it is respectfully submitted that it would not have been obvious to prepare a composition comprising human lower molecular weight GAD of at least 99% purity with a pharmaceutical carrier as claimed.

5. Claims 35 and 54-57 Would Not Have Been Obvious Under 35 USC 103(a) over US 4,086,142 in view of US 4,736,020

The '142 patent is cited as teaching a composition in pharmaceutically acceptable carrier comprising GAD (citing to col. 14, lines 14-16). The Examiner acknowledges that the reference does not teach that the composition is at least 99% w/w pure. The '020 patent is cited as teaching purity of a polypeptide to at least 99%. The Examiner takes the view that it would have been obvious to combine the teachings of the references in that purification of polypeptides to the desired purity was well-known in the art, and it would generally be preferable to use more pure reagents.

It is respectfully submitted that neither the feasibility of purifying proteins to 99% nor the general preference for use of pure reagents would have provided sufficient motivation to combine the teachings of the references. The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (BPAI 1993). An "assertion that one of ordinary skill in the relevant art would have been able to arrive at applicant's invention because he had the necessary skills to carry out the requisite process steps" is an "inappropriate standard for obviousness." *Orthokinetics Inc. vs. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). Here, the '020 patent purified TNF to at least 99% purity because it was intended for a pharmaceutical use (see col. 2, lines 10-12). The '142 patent does not disclose a pharmaceutical use for GAD, but rather proposes to use GAD as a chemical reagent to remove serum glutamate from serum as part of an in vitro analysis.

Whereas it is advantageous for a pharmaceutical agent to be purified to at least 99% purity to avoid possible side effects from contaminating materials, such a level of purity is not necessary in an in vitro reagent whose use involves no possibility of side effects. It is well known that increasing the degree of purity involves tradeoffs in terms of reduction in yield, and time and expense to effect the production. In the circumstances, it is submitted that the skilled artisan would not be impelled to perform additional steps to purify the GAD of the '142 patent to a level suitable for pharmaceutical use when no pharmaceutical use for GAD is disclosed by the '142 patent.

Moreover, the '142 patent does not disclose a composition suitable for parenteral use to a human as claimed. Claim 35 is directed to a composition comprising glutamic acid decarboxylase in a pharmaceutically acceptable carrier for parenteral administration to a human patient. The recitation "for parenteral administration to a human patient" is not merely a statement of intended use but also an implied constraint on the nature of the composition. For example, Remington's Pharmaceutical Sciences (of record and cited at p. 21, line 4 of the specification) in connection with preparation of parenteral compositions states at p. 1546 that:

An inherent requirement for parenteral preparations is they be of the very best quality and provide the maximum safety for the patient....Even the thought of using inferior techniques or ingredients in a manufacturing process must not be countenanced.

Thus, a composition for parenteral administration to a human must be *inter alia* sterile and substantially free of pyrogens and particulate matter (*id* at p. 1567). By contrast, a laboratory preparation of a protein is not typically sterile, and also usually contains impurities that would have been removed by sterilization and manufacture under GMP conditions.


Here, the preparation discussed by the '142 patent is disclosed as being "crude" and dissolved in a buffer of 20 mM acetate and pH 5.5 (col. 14, lines 14-16). This is a laboratory preparation suitable only for analytical use. The '142 patent does not disclose that the preparation was sterilized, free of pyrogens or particulate matter, or otherwise prepared in accordance with good manufacturing practices. In these circumstances, it would have been, at the very least, grossly irresponsible, and probably, illegal to administer parenterally the preparation of the '142 patent to a human patient. Accordingly, the '142 preparation cannot be considered to have been a composition for parenteral administration to a human patient.

Claims 54-57 are distinguished over the combination of cited references on additional grounds. The reference does not disclose lower molecular weight GAD, as recited in claim 54, recombinant GAD, as recited in claim 55, GAD synthesized on a peptide synthesizer as recited in claim 56, or GAD purified from the central nervous system, as recited in claim 57.

IX. CONCLUSION:

For the above reasons, appellants respectfully request that all rejections be reversed, and remanded for allowance of claims 54 and 59, and declaration of an interference between the present application and University of Florida, US 6,001,360 and US 5,762,937 for the remaining claims.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

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Appendix A Listing of pending claims

Claim 31 A method for inhibiting the development of insulin dependent diabetes mellitus, said method comprising administering to a patient a therapeutically effective dosage of glutamic acid decarboxylase (GAD).

Claim 35 A composition comprising glutamic acid decarboxylase, which is at least 99% w/w/ pure, in a pharmaceutically acceptable carrier for parenteral administration to a human patient.

Claim 50 The method of claim 31, wherein the GAD is recombinant GAD.

Claim 51 The method of claim 31, wherein the GAD is synthesized on a peptide synthesizer.

Claim 52 The method of claim 31, wherein the GAD is purified from the central nervous system tissue.

Claim 53 The method of claim 31, wherein the patient is a prediabetic patient having autoantibodies to GAD.

Claim 54 The composition of claim 35, wherein the GAD is lower molecular weight (GAD65).

Claim 55 The composition of claim 35, wherein the GAD is recombinant GAD.

Claim 56 The composition of claim 35, wherein the GAD is synthesized on a peptide synthesizer.

Claim 57 The composition of claim 35, wherein the GAD is purified from the central nervous system tissue.

Claim 59 The composition of claim 54, wherein the GAD65 is human GAD65.

Claim 62 A method of preventing or inhibiting the development of insulin dependent diabetes, wherein said method comprises administering to a patient at least 99% w/w pure GAD protein or a fragment thereof, which, when administered to the patient, prevents or inhibits the development of insulin dependent diabetes.

Claim 63 The method of claim 62, wherein the GAD protein or fragment thereof is a recombinant protein.

Claim 64 The method of claim 31, wherein the GAD is administered intravenously.

Claim 65 The method of claim 62, wherein the GAD or fragment is administered intravenously.

Claim 66 The method of claim 31, wherein the GAD is administered subcutaneously.

Claim 67 The method of claim 62, wherein the GAD is administered subcutaneously.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Steinunn Baekkeskov *et al.*

Application No.: 08/838,486

Filed: April 7, 1997

For: IMPROVED METHODS FOR THE
DIAGNOSIS AND TREATMENT OF
DIABETES

Examiner: G. Ewoldt

Art Unit: 1644

SECOND DECLARATION OF
STEINUNN BAEKKESKOV UNDER 37
CFR §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Steinunn Baekkeskov, state as follows:

1. I have previously submitted a declaration in these proceedings. My experience and qualifications are summarized in that declaration.
2. In the present declaration, I address an additional point raised in the final office action.
3. As discussed in my previous declaration and an accompanying Press Release, a phase II clinical trial is being conducted to test treatment of GAD on patients with a subtype of type II diabetes termed LADA (Latent Autoimmune Diabetes in Adults). A 6-month report on the trial provided evidence that administration of 20 micrograms GAD was safe and provided statistically significant evidence of efficacy over placebo ($p=0.0008$). Recently the 18-month data from the Phase II studies were released (Immunology of Diabetes Society's 7th Congress in Cambridge, England. The report showed that the positive effect on insulin production achieved six months after treatment still remains eighteen months after treatment and provided evidence that this effect is mediated by induction of regulatory T-cells (CD4+CD25+) (see attached press release of March 29, 2004). I understand the Examiner disregards the evidence obtained 6 months after

treatment on the basis that the trial was conducted on patients suffering from a "related pathology of non-autoimmune origin" (final office action at p. 4). This position is incorrect.

4. Patients with LADA subtype of type II diabetes are patients whose initial presentation of disease masquerades as type 2 diabetes because of its late onset, but whose underlying pathology including presence of autoimmune attack on GAD, is characteristic of type I diabetes (also known as IDDM) (see attached excerpt from DiabetesMonitor.com). Thus, the LADA subtype, as indicated by its name, Late Autoimmune Diabetes in Adults, is generally recognized as being a form of type I diabetes with a late onset. These patients undergo the same autoimmune destruction of beta pancreatic cells as other Type 1 patients, and are expected to benefit from immunotolerance by GAD therapy as other Type 1 patients. The reasons for starting prophylactic therapy in this group of patients rather than in asymptomatic children include that LADA patients regularly receive medical care, and that the clinical benefits can be detected more quickly (see attached press release). Both of these factors facilitate conducting a clinical trial

5. Because LADA patients undergo the same autoimmune destruction of beta pancreatic cells as other Type 1 patient, in my opinion, the results obtained in the phase II trial for treatment of LADA patients with GAD would also be expected for other Type 1 diabetes patients treated with GAD.

(6) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Steinunn Baekkeskov *et al.*
Application No.: 08/838,486
Page 3

PATENT

Respectfully submitted,


Steinunn Baekkeskov

Date 8/13/04

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Latent Autoimmune Diabetes in Adults is a form of type 1 diabetes which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes. It is frequently confused with type 2 diabetes.

Latent Autoimmune Diabetes in Adults (LADA) is a form of autoimmune diabetes (type 1A diabetes) which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes (that is, over 30 years of age at diagnosis). Alternate terms that have been used for "LADA" include Late-onset Autoimmune Diabetes of Adulthood, "Slow Onset Type 1" diabetes, and sometimes also "Type 1.5 [Type one-and-a-half]" diabetes.

Often, patients with LADA are mistakenly thought to have type 2 diabetes, based on their age at the time of diagnosis. Such misdiagnosis is easy to make when the person is older, and initially responds to treatment with diabetes pills. It is now thought that perhaps twenty percent of patients with apparent Type 2 diabetes really have LADA.

Patients with LADA do not have insulin resistance, as do people with Type 2. Also, positive antibody tests would help make the diagnosis of LADA in a person who might be suspected of having either LADA or Type 2.

Some diabetes specialists feel that once LADA is diagnosed, it is important to promptly start the patient on insulin therapy (rather than using sulfonylureas or other diabetes pills), but it is unclear whether early treatment with insulin is beneficial for the remaining beta cells.

Drug therapy to preserve insulin function in patients with LADA is being investigated.

Characteristics of LADA

- Adult age at diagnosis (usually over 25 years of age)
- Initial presentation masquerades as non-obese type 2 diabetes (does not present as diabetic ketoacidosis)
- Initially can be controlled with meal planning with or without diabetes pills
- Insulin dependency gradually occurs, frequently within months
- Positive antibodies
- Low C-peptide levels.
- Unlikely to have a family history of type 2 diabetes.

Also see:

- ★ [Type 1.5 Diabetes](#)
- ★ [Latent Autoimmune Diabetes in Adults](#) (PDF file)
- ★ [Autoimmune diabetes not requiring insulin at diagnosis \(latent autoimmune diabetes of the adult\): definition, characterization, and potential prevention.](#) (Abstract at PubMed)
- ★ [Progress in the characterization of slowly progressive autoimmune diabetes in adult patients \(LADA or type 1.5 diabetes\).](#) (Abstract at PubMed)
- ★ [New Drug Arrests Progression of Type 1 Diabetes](#)

Revised March 5, 2003

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Press Release

Stockholm, March 29, 2004

Diamyd reports increased long-term effect in diabetes pharmaceutical and carries out guaranteed new share issue

- 18-month data from the Phase II studies with Diamyd™ for the treatment of autoimmune diabetes shows that the positive effects achieved after six months remain and are increased. Furthermore, the mechanism, i.e. the underlying reason for the effect of Diamyd™, has been identified.
- These positive results are going to be of great importance in creating advantageous conditions in the Company's ongoing process of finalizing a licensing agreement with an industrial partner.
- To improve the Company's position even further in the ongoing discussions on licensing with a third party and to make continued development of the Company's patented GAD platform possible, on March 26, 2004 the Board decided to carry out a new share issue.
- If fully subscribed the Company will receive approximately SEK 92 million.
- The new share issue, conditional on the approval of an extraordinary general meeting on April 27, 2004, has been completely guaranteed by a consortium consisting of both existing shareholders and new institutional shareholders.
- The Board also intends to request authorization from the general meeting to accept over-subscription from the shareholders equivalent to 20% of the outstanding number of shares after the rights issue described above.

Long-term results from Diamyd Medical's Phase II study

At the IDS7 diabetes congress in Cambridge, England on March 29-31 2004, significant progress from the Company's Phase II studies with the diabetes treatment Diamyd™ is being presented.

Diamyd™ provides long-term effect

An earlier six-month report from the study (Lernmark, ADA, June 2003) showed that insulin production, normalized for glucose concentration, increased significantly in diabetes patients who were treated with 20 µg Diamyd™ compared with a placebo ($p=0.0008$). The results being presented at Cambridge show both the mechanism of the treatment's function and that the increased insulin production still remains at the improved level 18 months after the treatment. This data indicates that the autoimmune attack against the patient's insulin-producing cells has either been kept in check or stopped.

Evaluation of further parameters that verify the effect of the pharmaceutical preparation. Aiming to further verify the effect of the treatment, the Company has evaluated the changes in the average blood sugar levels (HbA1c). 18 months after the treatment with 20 mg Diamyd™, the results show a statistically significant improvement compared with a placebo ($p=0.009$). The change between the 20 mg dose group and the placebo group was about 20%, which is very positive as only a change of 5% is considered to have a significant importance for HbA1c.

The mechanism of the treatment has been identified and proved

The immunological mechanism underlying Diamyd™ treatment has been proved. The number of regulatory T-cells, measured as the T-cell quotient $CD4+CD25+/CD4+CD25-$, increased after 6 months in patients treated with Diamyd™ who showed increased insulin production ($r=0.56$; $p=0.001$). GAD specific regulatory T-cells are considered to cause a lowering of the autoimmune inflammation in the insulin-producing cells of the pancreas.

Carl-David Agardh, professor of diabetes research at Lund University, Sweden and head physician at the University Hospital, UMAS, in Malmö, Sweden and who is in charge of the study, says:

"The 18-month results confirm and strengthen the results obtained after 6 months. This is very promising. Patients in which we succeeded in maintaining their own production of insulin are expected to experience significantly reduced complications at a later date."

Target groups for Diamyd™ – autoimmune diabetes

There are various types of diabetes. Type 1 diabetes, insulin-dependent diabetes, is the type that normally appears in young people and that requires daily injections of insulin. Type 1 diabetes is an autoimmune disease, i.e. the immune system attacks and kills the body's own insulin-producing beta-cells. When about 85% of all the insulin-producing cells have been destroyed the remaining beta-cells cannot produce sufficient insulin and the patient is obliged to take daily insulin injections.

With type 2 diabetes the patient normally retains the ability to produce insulin. However the insulin has lost some of its potency – the insulin sensitivity has been reduced – which results in elevated blood sugar levels. These patients are often treated with pharmaceutical preparations in the form of tablets for their insulin sensitivity.

About 10% of all diabetics have a form of the disease that, simply put, is seen to lie between type 1 and type 2 diabetes. This form of the disease is called Latent Autoimmune Diabetes in Adults, LADA, and is a slowly progressive form of autoimmune diabetes that does not often appear before adulthood. LADA patients are identified as being diabetics who do not as yet need to take insulin injections but who have antibodies against GAD. This means that these patients have an autoimmune form of diabetes that results in their beta-cells successively being destroyed and that they thereby become dependent on insulin injections within a year or two.

"The first application for Diamyd™ is seen to be LADA patients" says Anders Essen-Möller, CEO of Diamyd Medical. "It is this group that has participated in the Phase II study. There are several reasons for this. The patients are adults, they already have diabetes and they regularly receive medical care. It is known that their beta-cells will be destroyed so that they will become dependent on insulin injections but even so they have more remaining beta-cells than type 1 patients. The sooner the treatment is started, the greater the chance of achieving appositive result. Furthermore, the LADA group is large when seen as a market and more than justifies the development of the pharmaceutical preparation from an economic point of view."

The next application is the treatment of new onset type 1 diabetes. The aim is to stop the autoimmune process that results in the destruction of the patient's remaining beta-cells with two injections of Diamyd™. Our long-term objective is to vaccinate children to prevent the disease.

"With the new, positive results and the guaranteed capital issue we can now lift the Company to a new level where we can evaluate new applications for our GAD technology at the same time as we can continue negotiations for licensing with a stronger capital base."

From pharmaceutical to vaccine

The Company's first applications with Diamyd™ is seen, as mentioned above, to be a treatment for LADA patients and also later for new onset type 1 diabetes patients so that they can retain their own insulin production. The long-term aim, however, is to develop a vaccine for whole groups of the population. "Major screening studies are underway around the world, among them all newly born babies in the Swedish region of Skåne, to try and identify those who run the risk of developing type 1 diabetes," says Åke Lernmark, Professor of Medicine at the University of Washington in Seattle, US. "Now we have found a possible mechanism for auto-gene treatment of LADA patients – we have shown that regulatory T-lymphocytes increase in patients in which the production of insulin increases – so I hope in the future to be able to treat children at risk at an early stage and to try and eliminate type 1 diabetes in children and young people.

Professor Lernmark is also Professor of Experimental Diabetes at Lund University, Department of Endocrinology at the University Hospital in Malmö. At an early stage Prof. Lernmark focused his attention on diabetes and the antigen that later proved to be GAD. He was one of the first to show the presence of antibodies against GAD in insulin-dependent diabetes. Prof. Lernmark has been a member of Diamyd Medical's Scientific and Medical Council since 1996.

Daniel Kaufman, Professor at the Department for Molecular and Medical Pharmacology at UCLA, showed in 1993 that giving GAD to mice that normally develop insulin-dependent diabetes prevented the outbreak of the disease. This research formed the basis of UCLA's patent portfolio around GAD and the fundamental patent was granted in the US as late as January 2004. The patent portfolio, for which Diamyd Medical has an exclusive license, therefore provides protection until 2021, According to Prof. Kaufman, who is a member of Diamyd Medical's Scientific and Medical Council: *"The vaccine to prevent type 1 diabetes arose from experiments at UCLA with diabetes-prone mice that were protected from developing the disease by vaccinating them with a protein from the insulin producing cells called GAD. It's tremendously satisfying to see our work at UCLA go from the lab to a clinical application with the potential to help so many people"*

Other applications for the Company's GAD technology platform

At present Diamyd Medical is developing the pharmaceutical based on the GAD65 (glutamic acid decarboxylase) technology platform for diabetes. The Company intends to evaluate the opportunities for R&D in the following areas:

Obesity

The GAD gene has been identified as the candidate gene for obesity. The Company intends to investigate the possibilities of developing a treatment for obesity based on GAD65.

Parkinson's Disease

GAD therapy is being investigated by another organization for treating Parkinson's disease. Diamyd Medical intends to issue a license for the GAD-based therapy for Parkinson's disease.

SMS

Antibodies against GAD have been found in patients with the rare movement inhibitory disease SMS. There is a possibility for applying for an Orphan Drug Status for the treatment of SMS. Diamyd Medical has devised a preclinical plan as a basis for carrying out small-scale clinical trials.

New Share Issue

The Board for Diamyd Medical AB (publ) has decided on a new share issue of a maximum of about SEK 92 million, equivalent to a maximum of 2,314,288 shares or the higher amount and number of shares (maximum 71,277 series B shares) that can follow because of subscription of shares supported by outstanding option rights. The issue price has been fixed at SEK 40 per share. Each even numbered share of series A and B gives the right to subscribe to a new share of series B. The rights issue decision is conditional on the approval of an extraordinary general meeting to be held on April 27, 2004 in Stockholm. In the event of the rights issue being fully subscribed, the Board also intends to request authorization from the extraordinary general meeting to carry out another new share issue of at most 1,431,327 shares, equivalent to 20% of the outstanding number of shares after the rights issue described above, at an issue price of SEK 40 per share.

The issue in its entirety has been guaranteed by a declaration of intent from a consortium consisting of both existing shareholders and a number of new institutional owners. Existing shareholders shall have preferential subscription rights.

This new share issue strengthens the Company's position as a credible and long-term partner for industrial players. At the same time the Company's position is strengthened in ongoing negotiations for the issuing of a license for Diamyd™. Furthermore, the emission gives the Company the possibility of further developing the Company's GAD platform within the framework of the strong patent portfolio.

The positive results from the Phase II study provide the possibility of evaluating and developing new, potential pharmaceutical candidates, not only for the treatment of diabetes but also for other metabolic and neurological diseases.

Schedule

Extraordinary general meeting	April 27, 2004
Final day for share trading with right to participate in the new share issue	April 29, 2004
Record day for right to participate in the new share issue	May 4, 2004
Trade with subscription rights	May 7 - 25, 2004
Subscription period	May 7 - 28, 2004

A prospectus is expected to be available during the week starting May 3.

ABG Sundal Collier AB is advisor to the Company in the capital rights issue in question.

Stockholm March 26, 2004

Diamyd Medical AB
The Board

For further information, please contact:

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Originator Drug Development

RICHARD J. FINDLAY *

This article will cover a few issues in originator drug development. First, this article will build on the textbook drug development timeline introduced earlier¹ by Gerald Mossinghoff, in order to refresh some memories on some of the terminology, but more exactly to provide where some of the timeline references have come from so that one can actually work with those references directly. Second, there will be a basic discussion of some data that shows how variable this timeline can be in originator and generic drug development. The majority of the session, however, will cover commercial practices since 1984 and how the balance sought by the Hatch-Waxman Act² has been achieved by the originators, the branded pharmaceutical companies, and the generic companies.

Figure 1 (see following page) provides a more detailed look at the types of trials actually performed during the stages of the originator drug development process, and the actual time necessary to develop a drug.³ Several things should be highlighted. One sees that the drug discovery and development process takes approximately 14.7 years as compared to sixteen years, as was discussed earlier. The difference occurs mainly in the discovery period. Indeed, it is very difficult to estimate what will happen in the discovery stage. What is discovery? Is it somebody just sitting down with a piece of paper? When does discovery really start?

In examining figure 1 (see following page), one can see the phases of drug development. For instance, during the early research and preclinical testing period, the originator performs pharmacological screening and tests on pharmacodynamics, pharmacokinetics, toxicokinetics, acute toxicity, subchronic toxicity, and genotoxicity prior to applying for investigational new drug (IND) status. During the clinical testing period, originators conduct tests for safety in Phase I, efficacy in Phase II, and for side effects and long-term use effects in Phase III (testing such things as chronic toxicity, carcinogenicity, reproductive toxicity, additional genotoxicity, and special toxicity) prior to submitting a new drug application (NDA) and receiving Food and Drug Administration (FDA) approval. After FDA approval, postmarketing testing continues in Phase IV for, *inter alia*, side effects, clinical education, and possible new indications.

In practice, the time variability for originator product development is wide. Pre-clinical testing may require from thirty to fifty-seven months; Phase I may take from ten to eighteen months; Phase II may take from twenty-one to thirty-five months; Phase III may take from twenty-eight to fifty-five months; and FDA approval may take from six to 114 months.⁴ Thus, one of the most significant time variations occurs

* Mr. Findlay is Vice-President, Health Care Practice, A.T. Kearney, Inc., New York, NY.

¹ Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 193 (1999).

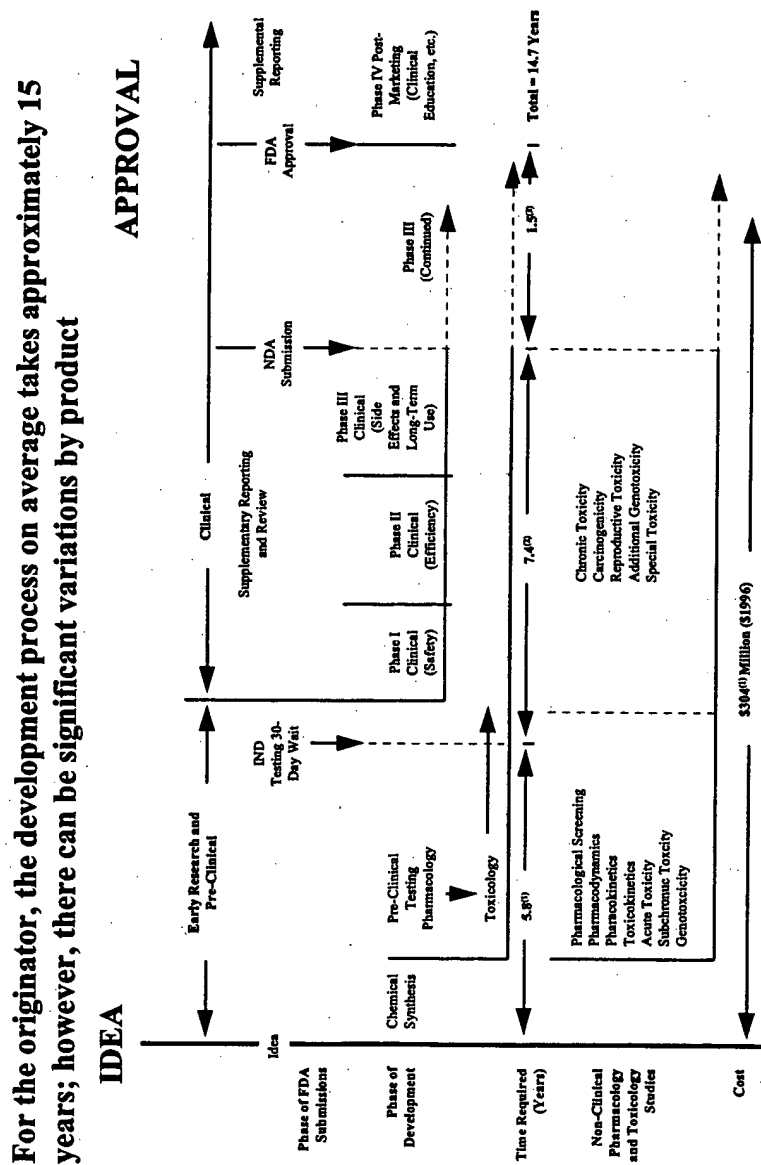
² Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994)).

³ The Center for the Study of Drug Development, located at Tufts University, is the source for the figures on drug development times and costs. The main chart was published by Parexel, a leading contract research organization, in MARK MATHIEU, *NEW DRUG DEVELOPMENT: A REGULATORY OVERVIEW* 19 (rev. ed. 1998). The book is a helpful source of information for those doing drug development and clinical work.

⁴ The source for this data is work done internally at A.T. Kearney, Inc., plus some data that is published by the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs.

in the approval process. One reason an originator can be approved quickly is that a company can apply for a "rolling" NDA; although it does not file, the company extensively discusses the submission and resubmissions with FDA. When the company does file, essentially it has a perfect file.

Figure 1 Originator Product Development Timeline



Notes: (1) Figure indexed from Tufts Centers for the study of drug development (CSDD) data on mean time from synthesis to FDA approval (1990, 1995)
 (2) Mean clinical development time to new chemical entities (NCE) approved in 1995 (source Tufts CSDD)
 (3) Mean approval time for 1996 approval NME (Source FDA)

Source: Tufts CSDD

The generic drug development process can take three to five years, with the abbreviated new drug application (ANDA) approval process being the greatest time variable.⁵ It is very difficult, however, to know exactly what generic companies do in product development. In a typical generic product development cycle, a generic company commits resources to target a product three to five years before the originator patent expires. Product development usually takes six to eighteen months, with bioequivalence testing taking another six to twelve months. ANDA approval takes approximately eighteen to thirty months,⁶ dependent on the number of times the Office of Generic Drugs (OGD) rejects the application and requires additional tests and/or data to be filed.

Important aspects of the generic drug development process include:

- up-front investment of \$1,000,000;
- making or buying the active ingredient;
- developing a formulation;
- testing product;
- setting standards (usually based on the U.S. Pharmacopoeia and publicly available information); and
- product approval, which virtually always takes multiple review cycles (each cycle takes six months or more).

The timeline for a generic company is much shorter for two reasons. First, the company is targeting a defined product that probably has been on the market for at least five, if not ten, years. After that, one needs to do bioequivalence testing, which is the main FDA requirement as the result of the Hatch-Waxman Act.⁷ Second, the dynamics of the compound under study are fairly well known — making it relatively easy to undertake product formulation and development.

It is understating the case, however, to say that it only takes about three to five years of commercial commitment by the generic company to produce a drug. Often generic companies begin preparations to compete about seven years before the patent expires or exclusivity ends. They would then be free to market the product without infringement after the expiry date. Thus, the generic companies initiate efforts about seven years before the expiry date to determine what strategies to employ and what opportunities might be available.

Originator companies looking to manage the late lifecycle of their products should be strategizing seven or ten years before loss of exclusivity. Originators should be very active in protecting their patents, whether in this country or anywhere in the world, against potential generic competitors seven to ten years out. If the litigation is high profile and vigorous, the generic manufacturer will have greater uncertainty as to the factors that it has to roll into its forecast, and what it will have to invest. Thus, the risk factors in a generic company's forecasts increase, which might deter the company from proceeding or may slow progress. Delay may range from three to six months to a maximum of a couple of years, as the generic company tries to anticipate the potential legal battles it could face.

The other aspect of concern is the paragraph IV filing⁸ — this must be sent not

⁵ *Id.*

⁶ The source of this information is trade information, the Office of Generic Drugs, and A.T. Kearney, Inc. interviews.

⁷ See 21 U.S.C. § 355.

⁸ *Id.* § 355(b)(2)(A)(iv) (FDCA § 505(b)(2)(A)(iv)).

only to FDA, but also to the patent holder. If there is no patent to be disputed, however, it is a paragraph III situation⁹ and no advising is necessary. In addition, FDA is required to keep that information confidential until approval time. In such circumstances, how does an originator know that somebody is contemplating a generic application? When the Office of Generic Drugs reviews the first application, it will publish and put in the public domain a critique of the bioequivalence protocol. It publishes the criticism as an indication to other companies that wish to file (or have filed) what the standards are for the product (and as a consequence any other generic manufacturer) to meet. Thus, OGD does not have to go back and negotiate every single application — it simply puts something on the record stating its questions or amendments to the first filed protocol. The issuance of such a protocol critique signals that a generic actually has filed an ANDA, and that an originator's drug will be in contention.

Originators also become aware, when that amendment or recommended amendments to the protocol are published, of the sort of issues that may raise questions for the ANDA filer concerning the validity of the bioequivalence testing. Indeed, it is such bioequivalence data that forms the core of an ANDA filing. The other aspect to emphasize is that this is primarily a process for small molecules — for the most part, there is no ANDA process for a biological product.

One additional issue to consider under the Hatch-Waxman definition is when the clock starts to run. The clock does not start running until one actually files an IND application, which is basically the Phase I work. Before that, however, one must expect some variability — a scientist could be doubling the time spent to get through this stage. Although that development does not count in terms of getting an extension, it is already taking time out of the patent life. One lesson and strategy to be learned, without prejudicing any NDA issues or the safety of the volunteers that will be taking part, is that in the first part of Phase I an originator needs to review how much pre-clinical work is necessary before filing. Some preclinical work actually is duplicative to some Phase I testing, thus, to gain the benefits of the Hatch-Waxman extension, it is preferable to perform it during Phase I.

For generic products, variability in approval time is related to the strategy employed and the completeness of the generic ANDA. Formulation may take from six to eighteen months; bioequivalence testing may take from six to twelve months; ANDA queries and resubmissions, if necessary, may take up to twenty-four months; and approval may take from six to thirty months.¹⁰ Indeed, one of the most significant periods in terms of time variability is the approval stage and that is because the OGD on average rejects a filing approximately two times out of three.¹¹ It takes about six months for the company to satisfy those queries and resubmit. Thus, the average approval time is approximately twenty-two months, although OGD is trying to target approval in about twenty months.

Generic companies have an incentive to do as little as possible before filing and entering the cycle of amendments, because they often are filing between three to five years before the patent expires. Thus, they have time to go through those amendment cycles. Because the OGD suffers from chronic understaffing and does not have a user fee arrangement similar to that of originator companies for a full NDA filing, an ANDA could stay in OGD for months, even years, before it is examined.

In commercial practice, various strategies can be employed by originator phar-

⁹ *Id.* § 355(b)(2)(A)(iii) (FDCA § 505(b)(2)(A)(iii)).

¹⁰ Data compiled by A.T. Kearney, Inc.

¹¹ Data compiled by A.T. Kearney, Inc.

maceutical companies to try to extend the patent term or reduce the degree of competition from generics to maximize value.¹² Generally, the value maximization tactics fall into four categories: extending exclusivity, minimizing the impact of competition, transferring value, and expanding the client base for the drug.

The first category consists of strategies to extend exclusivity. The classic example is Procardia® and Procardia-XL® from Pfizer. With Procardia®, the original patent expired on nifedipine, but before the patent expired Pfizer brought in an extended-release form of the product. The extended-release technology had its own patent life, therefore the Procardia® patent was extended until the expiry of patent protection on the technology for extended-life formulation. Besides developing a new patented delivery system, other strategies for extending exclusivity include:

- obtaining a manufacturing process patent;
- extending exclusivity through clinical trials;
- extending a patent through legal challenge; and
- obtaining a patent for a purified version of the product.

In the second category, strategies try to minimize the impact and penetration of generic compounds once they are launched. Most strategies try to strengthen prescribers' brand loyalty for the originator drug. With increased ability to access consumers directly with television and other advertising, originators attempt to tie the patient more closely to the originators' brand. Also included in this category are some technical strategies, particularly the use of tighter bioavailability standards. That was a strategy successfully pursued by SmithKline Beecham with Diazide®, until certain generic competitors acted fraudulently to replicate the needed bioequivalency data. Other methods in this category include launching a patient compliance program and the originator choosing to enter the generic market.

A third set of strategies transfers the value to a new product, which usually occurs when one has a franchise with a drug whose patent is expiring. The company launches a next generation product and transfers loyal prescribers from the existing product to the new product. Also in this category of strategic options is transferring loyalty from the prescription drug to an over-the-counter (OTC) version of the drug. One final tactic in this category is to market a second drug in the same therapeutic class. This tactic is based on the theory that by selling two similar drug products now, which theoretically would double current sales, an originator can retain twice as much market share later, when future sales fall because of generic competition.

The fourth set of strategies focuses on expanding the client base and includes:

- increasing price;
- expanding into new markets;
- increasing marketing efforts; and
- forming long-term contracts.

For generic companies, the industry has seen a very dramatic increase in the speed and extent to which generics' penetrate the market, with eventual market penetration rates ranging from forty-five percent for Syntex's Naproxen, which lost patent cover 1993, to eighty percent for SmithKline Beecham's Cimetidine and BMS' Captopril, which lost patent cover in 1994 and 1997, respectively.

¹² A.T. KEARNEY, INC., PATENT EXPIRY AND THE BATTLE AGAINST GENERICS 7 (1998); Richard J. Findlay, *A Compelling Case for Brand Building*, PHARM. EXEC., Feb. 1998, at 76.

For originators, competition within any therapeutic class has increased significantly, irrespective of patent validity, due to market entry of therapeutically-equivalent products with different chemical structures. One reason for this increased competition is a drug industry that is now better defined in terms of its technology and has a better understanding of the regulations and the process to bring a product to market. Because of user fees and greater regulatory transparency, however, it is easier for a major originator company to structure an approach and get approval. In addition, for originator products, exclusivity periods have shortened over time, from ten years in 1968 to one year in 1992.¹³

Finally, competition among generic manufacturers themselves has become a greater issue because the Hatch-Waxman Act not only opened the market to a generic competitor, it lowered the investment barrier to a level where any company can compete. A.T. Kearney research shows, not surprisingly, that the more generic competitors that enter the market, the faster and more significant is price erosion.¹⁴ Capropril provides the best example of this; on the first day of generic launch there were twelve companies selling it at ten or twenty percent of the originator's price. At such price levels it is questionable whether generic manufacturers can make sustainable profits, thus bringing into question the long-term viability and competitiveness of the generic manufacturing industry.

¹³ See *supra* note 4.

¹⁴ Research and analysis by A. T. Kearney, Inc.